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(54) Oral Contraceptive Formulation

(72) Casper, Robert F. , Canada

(73) Jencap Research Ltd. , Canada

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ABSTRACT 1332227

This invention is concerned with a contraceptive formulation which employs a combination of estrogen and progestin and wherein a short period of relatively dominant estrogenic activity alternates with a short period of relatively dominant progestagenic activity.

ORAL CONTRACEPTIVE FORMULATION

This invention is concerned with a contraceptive formulation and a method of contraception which employs a combination of estrogen and progestin and wherein a short period of relatively dominant estrogenic activity alternates with a short period of relatively dominant progestagenic activity.

In the luteal phase of the menstrual cycle, serum progesterone levels increase and progesterone mediated secretory changes occur in the uterine endometrium. The presence of progesterone receptors has been shown to be a necessary prerequisite for progesterone action in the endometrium (see Walters, M.R. and Clark, J.H. Relationship between the quantity of progesterone receptors and the antagonism of estrogen-induced uterotropic response Endocrinology 105:382, 1979) and it is well documented that estrogen priming in the follicular phase of the cycle is responsible for the development of both estrogen and progesterone receptors (see Bayard, F., Damilano, S., Robel, P. and Baulien, E.E. Cytoplasmic and nuclear estradiol and progesterone receptors in human endometrium, J. Clin Endocrinol Metab. 46:635, 1978). On the other hand, progesterone exerts a negative feedback effect on its own receptor (see Tseng, L. and Gurpide, E. Effects of progestins on estradiol receptor levels in human endometrium, J. Clin Endocrinol Metab. 41:402, 1975) and also acts to downregulate endometrial estrogen receptors possibly by induction of an estrogen receptor regulatory factor (see Leavitt, W.W., Okulicz, W.C., McCracken, J.A., Schramm, W.S. and Robidoux, W.F. Jr. Rapid recovery of nuclear estrogen receptor and oxytocin receptor in the ovine uterus following progesterone withdrawal, J. Steroid Biochem. 22:686, 1985).

These physiologic changes can be reproduced pharmacologically as shown by the induction of estrogen and progestin receptors in postmenopausal women by the administration of ethinyl estradiol (see Kreitmann, B., bugat, R. and Bayard, F. Estrogen and Progestin Regulation of the Progesterone Receptor Concentration in Human Endometrium, J. Clin Endocrinol Metab. 49:926, 1979). Neumannova et al (see Short-Term Effects of Tamoxifen, Medroxy-progesterone Acetate, and Their Combination on Receptor Kinetics and 17beta-Hydroxysteroid Dehydrogenase in Human Endometrium, Obstet. Gynecol. 66:695, 1985) have also demonstrated that administration of medroxy-progesterone acetate in estrogen-primed women decreases the concentration of endometrial progestin receptors while at the same time increasing the activity of 17beta-hydroxysteroid dehydrogenase, an enzyme which is responsible for metabolism of estradiol to the less potent estrone.

A complex interaction occurs between estrogen and progesterone or progestin in the human endometrium with the progestins acting as anti-estrogens. Estrogen and progestin interactions are also dynamic. For example, estrogen administration increased the concentration of both estrogen and progestin receptors to peak levels, 7 times above baseline, within 3 days (see Ekert, R.L. and Katzenellenbogen, B.S. Human Endometrial Cells in Primary Tissue Culture: Modulation of the Progesterone Receptor Level by Natural and Synthetic Estrogens In Vitro, J. Clin Endocrinol Metab. 52:699, 1981). A three-fold increase in receptor concentrations occurred within one day. Normal physiologic levels of progesterone in the first 3 days of the luteal phase resulted in a rapid and significant decrease in estrogen receptor number (see

Kreitmann-Gimbal, B., Bayard, F., Nixon, W.E. and Hodgen, G.D. Patterns of Estrogen and Progesterone Receptors in Monkey Endometrium During the Normal Menstrual Cycle, Steroids 35:471, 1980). Exogenous administration of progesterone to cynomolgous macaques significantly suppressed estrogen receptors within 1 to 2 days (see West, N.B. and Brenner, R.M. Progesterone-Mediated Suppression of Estradiol Receptors in Cynomolgous Macaque Cervix, Endometrium and Oviduct During Sequential Estradiol-Progesterone Treatment, J. Steroid Biochem. 22:29, 1985) and medroxy-progesterone acetate was able to significantly suppress progestin receptor levels in premenopausal women within 4 hours (see Neumannova M., Kauppila, A., Kivinen, S. and Vihko, R. Short-Term Effects of Tamoxifen, Medroxy-progesterone Acetate, and Their Combination on Receptor Kinetics and 17beta-Hydroxysteroid Dehydrogenase in Human Endometrium, Obstet. Gynecol. 66:695, 1985). In contrast, progesterone withdrawal in the presence of constant estrogen levels has been shown to result in rapid (6 to 12 hours) recovery of nuclear estrogen receptors in sheep endometrium, associated with an estrogen induced biological response, i.e. production of oxytocin receptors (see Leavitt, W.W., Okulicz, W.C., McCracken, J.A., Schramm, W.S. and Robidoux, W.F. Jr. Rapid recovery of nuclear estrogen receptor and oxytocin receptor in the ovine uterus following progesterone withdrawal, J. Steroid Biochem. 22:686, 1985). A similar phenomenon occurs in pregnant guinea pigs when estrogen levels rise relative to progesterone levels prior to parturition (see Alexandrova, M. and Soloff, M.S. Oxytocin receptors and parturition in the guinea pig, Biol. Reprod. 22:1106, 1980).

Therefore, it appears that estrogen acts to stimulate both estrogen and progestin receptor concentrations and to induce sensitivity of the endometrium to both estrogen and progestin. Progesterone or progestin exerts an anti-estrogen action by decreasing estrogen receptors and by increasing 17beta-hydroxysteroid dehydrogenase activity in endometrial tissue. However, it appears that the stimulatory effects of progesterone on human endometrial function are of short duration probably because of a self-provoked downregulation of progestin receptors and estrogen receptors. For example, the effect of progesterone on 17beta-hydroxysteroid dehydrogenase peaks at 3 days and is then followed in 2 to 3 weeks by suppression of the enzyme (see Whitehead, M.I., Townsend, P.T., Pryse-Davies, J. et al. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium, N. Engl, J. Med 305:1599, 1981).

Currently on the market there are a number of contraceptive formulations which can be classified readily into several general types. The first of these are known as monophasic formulations. These contain a constant amount of estrogen and progestin. Nuisance side effects with these pills depend on the balance between the estrogen and progestin component of the pill. For example, with a relatively dominant progestin pill, the formulation will, over time, result in a depletion of both estrogen and progestin receptors. The result which might be expected is an understimulated or atrophic endometrium which may eventually cause either on-pill amenorrhea or breakthrough bleeding or spotting due to poor epithelialization. On the other hand, with a relatively dominant estrogenic preparation, it is possible that

prolonged use could result in endometrial growth with the development of unsupported fragile stroma and subsequent spotting or breakthrough bleeding.

Newer formulations known as triphasics have varying levels of estrogen and progestin; in most cases consisting of relatively constant levels of estrogen with a step-wise increase in progestin throughout the cycle. This pattern of estrogen and progestin administration results in a relatively dominant estrogenic formulation at the beginning of the package with increasing progestagenic activity toward the end of the package. Endometrial stability may be better with these pills since the estrogenic activity at the beginning of the package induces both estrogen and progestin receptors making the endometrium sensitive to the increased levels of progestin towards the end of the package. The progestin activity produces denser, more stable endometrial stroma although the relatively long duration of progestin exposure, toward the end of the package, may still lead to decreased estrogen and progestin receptors and activity. A significant problem with this type of formulation is the low dose of steroids at the beginning of the package which makes these pills vulnerable to drug interactions or missed pills which may lead to breakthrough ovulation. The beginning of the package is the critical time in terms of breakthrough ovulation since the user has just completed a 7 day drug-free interval during which follicular development may begin. Even if pregnancy does not occur, breakthrough ovulation can lead to poor cycle control.

The present invention provides a contraceptive preparation for administration to a woman comprising a series of from 20 to 35 consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of at most four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting extrogen activity sufficient to promote the development of progestin receptors in the endometrium of a woman to whom said preparation is administered, and the daily unit doses of said progestin dominant phases contain said substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity sufficient to antagonize the effect of estrogen on the endometrium of a woman to whom said preparation is administered and wherein each daily unit dosage includes a pharmaceutically acceptable inert carrier when required.

In another aspect, the invention provides a contraceptive package containing a total dosage regimen of 20 to 35 consecutive daily unit doses in orally administrable tablet form arranged in said package in a fixed sequence corresponding to an intended order of administration in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of at most four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity sufficient to promote the development of progestin receptors in the endometrium of a woman to whom said doses are administered, and the daily unit doses of said progestin dominant phases contain substance exhibiting estrogen activity and an amount of a substance exhibiting

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progestin activity sufficient to antagonize the effect of estrogen on the endometrium of a woman to whom said doses are administered and wherein each daily unit dosage includes a pharmaceutically acceptable inert carrier when required.

In a final aspect, the invention provides the use of a contraceptive formulation for administration to a woman of childbearing age comprising a series of from 20 to 35 consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of at most four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity sufficient to promote the development of progestin receptors in the endometrium of said woman, and the daily unit doses of said progestin dominant phases contain a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity sufficient to antagonize the effect of estrogen on the endometrium of said woman and wherein each daily unit dosage includes a pharmaceutically acceptable inert carrier when required.

In its basic aspect, the invention provides a pharmaceutical preparation for contraceptive purposes comprising a series of from twenty to thirty-five consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of from one to four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity or an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, and the daily unit doses of said progestin dominant phases contain an amount of a substance exhibiting estrogen activity and an amount of a

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substance exhibiting progestin activity, the amount of said substance exhibiting progestin activity being alternately increased in the progestin dominant phases to provide daily unit doses exhibiting progestin dominant activity and decreased in the estrogen dominant phases to provide daily unit doses exhibiting estrogen dominant activity and wherein the amount of substance exhibiting estrogen activity per unit dose exhibits an estrogen activity equivalent to from about 0.02 to about 0.050 mg of 17α-ethinyl estradiol and the amount of substance exhibiting progestin activity per unit dose ranges from 0 to an amount which exhibits a progestin activity equivalent to about 1 mg of norethindrone and wherein each unit dose contains a pharmaceutically acceptable inert carrier when required. Other basic aspects include the package and use forms of the contraceptive preparation.

It should be noted that the number of unit doses per phase preferably comprises from two to four unit doses.

In a preferred form of the invention, dominant estrogen activity dosages are used to begin and end the twenty to thirty-five unit dosages.

Preferred methods involve twenty-one and twenty-four unit dosages.

In another aspect of the invention, there may be included an additional seven unit dosages in the pharmaceutical preparation which may comprise a placebo or any other hormone-free agent.

The formulation of the present invention results in better cycle control. Intermittent increases in estrogen

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activity stimulate endometrial growth and progestin receptors. This makes the endometrium more sensitive to subsequent progestin activity which limits growth by decreasing estrogen receptors and increasing 17beta-hydroxy-steroid dehydrogenase. Interaction of progestin with progestin receptors induces secretory changes in the endometrium which results in a denser stroma and endometrial stability. A return to relatively dominant estrogenic activity then again stimulates estrogen and progestin receptors and renews endometrial sensitivity to progestin. This push/pull activity keeps endometrial activity within a narrow range depending on the number of days of estrogenic and progestagenic activity.

The design of the present invention avoids low levels of steroids present during the first part of the triphasic package which makes the triphasic formulations more sensitive to drug interactions and missed pills. As a result, less pill failures in terms of pregnancy occur and also cycle control is better because of fewer breakthrough ovulations.

The current formulation allows better progestational effect with less progestin. With the current formulation the dose of progestin is significantly decreased compared to most monophasic preparations and a total steroid dosage is achieved which is lower than that of the present triphasics and yet the present formulation offers better cycle control and efficacy. A reduction in progestin dosage results in less negative impact on HDL cholesterol levels. HDL cholesterol has been shown to be protective against development of atherosclerosis and its concentration is increased by estrogen and decreased by progestin.

Alternatively, the reduction in progestin dose possible with the subject formulation results in a pill that also has good estrogenic effect. Therefore, this formulation is a good one for the management of acne, oily skin and hirsutism and also has less chance of on-pill amenorrhea.

It is thought that the current formulation is better able to inhibit ovulation with lower doses of steroids, since it has been demonstrated that estrogen priming increases progesterone receptor concentration in the hypothalamus and anterior pituitary gland in a number of animal species (see Katzenellenbogen, B.S. Dynamics of steroid hormone receptor action, Annual Rev. Physiol. 42:17, 1980). Therefore, by allowing intermittent estrogenic priming to occur by administering the preparation of estrogen and progestin in the alternating fashion of the present method, it is possible to potentiate the central negative feedback actions of both progestin and estrogen.

The estrogens which may be employed as a component in the contraceptive regimen of this invention may be any of those conventionally available. Typically, the estrogen may be selected from the group comprising synthetic and natural estrogens. The synthetic estrogens may be selected from, for example, ethinyl estradiol, mestranol and quinestranol. Particularly of interest are 17alpha-ethinylestradiol and esters and ethers thereof. The preferred estrogen is 17alpha-ethinylestradiol. The natural estrogens may include, for example, conjugated equine estrogens, estradiol-17beta, estradiol valerate, estrone, piperazine estrone sulphate, estriol, estriol succinate and polyestrol phosphate.

The progestin component may be any progestationally active compound. Thus, the progestin may be selected from progesterone and its derivatives such as, for example, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17alpha-ethinyltestosterone and derivatives thereof, 17alpha-ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone, levo-norgestrel, dl-norgestrel, d-17alpha-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene, desozestrel and norgestimate. Preferred progestins are norethindrone, levo-norgestrel and norgestimate.

In a preferred form of the invention, the plurality of dosages may comprise from one to four unit dosages, but preferably three unit dosages are employed. Thus, in a preferred form of the invention, three unit dosages of relatively dominant estrogen activity are alternated with three unit dosages of relatively dominant progestin activity and so on for a total of twenty to thirty-five unit dosages. The last seven unit dosages which are free of hormone may be included to approximate the natural twenty-eight day menstrual cycle of the female. These pills may comprise a placebo or any other hormone-free agent. Examples of suitable alternative agents include vitamins, such as iron supplements where the total unit dosages do not comprise multiples of three, an appropriate number of hormone-free unit dosages may be included to make up the total required units.

Generally, the quantities of estrogen and progestin incorporated in the formulation of the invention are dependent on the type of estrogen or progestin selected.

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However, the quantities employed are generally less than those used in the currently marketed formulations for reasons mentioned earlier. In the present formulation, the estrogen level is kept at a constant level, while the progestin level is adjusted up or down to produce the required estrogen or progestin dominance. The selection of quantity is dependent on the type of estrogen or progestin since each hormone has its own specific activity.

Typically for the contraceptive formulation, the amount of estrogen per unit dose may range from a minimum of about 0.020 mg. to a maximum of about 0.050 mg. of 17alpha-ethinylestradiol or its equivalent dosage in other synthetic or natural estrogens and the amount of progestin per unit dosage may range from a minimum of about 0.00 mg. of norethindrone or its equivalent in a synthetic or natural progestin to a maximum of about 1.00 mg. Thus, the maximum amount of hormone over the 21 days of administration may range from about 6.72 mg. to about 22.05 mg.

Some preferred combinations include the following:

1. Three unit dosages of 0.035 mg. of 17alpha-ethinyl-estradiol with 0.5 mg. of norethindrone, alternating with three unit dosages of 0.035 mg. of 17alpha-ethinylestradiol with 0.75 mg. of norethindrone for a total of 7 groups of three, beginning and ending with the 0.5 mg. of norethindrone combination.

2. Three unit dosages of 0.035 mg. of 17alpha-ethinyl-estradiol and 0.5 mg. of norethindrone alternating with three unit dosages of 0.035 mg. of 17alpha-ethinyl- estradiol and 0.35 mg. of norethindrone, beginning and ending with the 0.5 mg. of norethindrone combination.

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The formulations of the invention may be administered orally, preferably in tablet form, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally. The method of administration determines the types of estrogens and progestins useful in the formulation, as well as the amounts per unit dosage.

Methods for transdermal administration including the associated methods for manufacturing such systems are well known in the art. In this connection, reference may be had to U.S. Patents Nos. 4,752,478, 4,685,911, 4,438,139 and 4,291,014.

Generally speaking, the formulations are prepared according to conventionally known procedures in accordance with the method of administration. Thus, the active ingredients are prepared according to known methods in a pharmaceutically acceptable form for administration. These ingredients, in their required quantities are combined with the appropriate pharmaceutical carriers such as additives, vehicles and/or flavour ameliorating substances. These substances may be referred to as diluents, binders and lubricants. Gums, starches and sugars are also common terms. Typical of these types of substances or excipients are pharmaceutical grades of mannitol, lactose starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like. The active ingredient(s) may comprise from about 0.01% by weight to about 99.99% by weight of the total formulation and the remainder comprises the pharmaceutically acceptable carrier. The percentage of active ingredient(s) may vary according to the delivery system or method of administration and is chosen in accordance with conventional methods known in the art.

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Thus, the active ingredients are compounded with the chosen carrier and in for example the case of a tablet form, placed in a tablet molding apparatus to form the tablets which are subsequently packaged in accordance with the chosen regimen.

In the oral form of the formulation, the contraceptives are preferably produced in the form of a pharmaceutical kit or package, with the daily dosages arranged for proper sequential administration. Thus, in another aspect, the present invention also provides a pharmaceutical package which contains combination-type contraceptives in multiple dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

Preferably, such packages are in the form of a transparent package with twenty-eight dosage units arranged sequentially and consisting of twenty-one or twenty-four tablets containing the combined estrogen/progestin formulation set up for the cyclical regimen of the invention and seven or four placebos thereafter.

Preferably the placebo tablets and tablets containing the hormones are different colours or shapes. Data indications may be provided on the packaging. The packaging may be a tube or box or a strip. The box may be circular, square, or otherwise shaped with the tablets being accommodated separately therein for ease of administration. Date indications may appear adjacent each tablet corresponding with the days on which each tablet is to be taken. Some indication of the sequence in which the tablets are to be taken preferably appears on the packaging regardless of its form.

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In the following examples, specific embodiments of the present invention are set forth. These are meant to be illustrative of the invention and are not meant to limit it in any way. All parts and percentages are by weight, unless indicated otherwise.

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EXAMPLE 1

Three-day phases of daily unit dosages of 17alpha-ethinyl-estradiol(EE) 0.035 mg. and norethindrone (NET) 0.5 mg. alternating with three-day phases of daily unit dosages of EE 0.035 mg. and NET 0.75 mg. for a total of 7 phases (21 days or 21 daily unit dosages) beginning and ending with the NET 0.5 mg. combination.

EXAMPLE 2

Three-day phases (daily unit dosages of EE 0.035 mg. and NET 0.5 mg.) alternating with three-day phases of daily unit dosages of EE 0.035 mg. and NET 0.35 mg., beginning and ending with the 0.5 mg. combination.

EXAMPLE 3

Two-day phases of daily unit dosages of EE 0.035 mg alternating with two-day phases of daily unit dosages of EE 0.035 mg and NET 0.35 mg, beginning and ending with the first unit dosage and running for 24 days total.

EXAMPLE 4

Three-day phases of daily unit dosages of EE 0.035 mg and NET 0.15 mg alternating with three-day phases of daily unit dosages of EE 0.035 mg and NET 0.35 mg and running for 24 days total.

EXAMPLE 5

Three-day and four-day phases of each of the above combinations as set forth in Examples 1 and 2, starting with either three- or four-day phases and ending with the other.

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EXAMPLE 6

Four-day and three-day phases of each of the above are prepared, starting with a four-day daily unit dosage of 0.5 mg. NET and 0.035 mg. EE and ending with a three-day daily unit dosage of 0.75 mg. NET and 0.035 mg. EE.

EXAMPLE 7

Three-day and four-day phases of each of the above formulations starting with a three-day phase of daily unit dosages of 0.35 mg. NET with 0.035 mg. EE and ending with a four-day phase of daily unit dosages of 0.5 mg. NET and 0.035 mg. EE.

EXAMPLE 8

One-day alternating phases using the daily unit dosages set forth in Examples 1 and 2.

EXAMPLE 9

Two-day alternating phases ending or beginning with a single three-day phase, using the daily unit dosage formulations set forth in Examples 1 or 2.

EXAMPLE 10

Three-day phases of daily unit dosages of EE 0.035 mg. and levonorgestrel (d-norgestrel) 0.05 mg. alternating with three-day phases of daily unit dosages of EE 0.035 mg. and levo-norgestrel 0.075 mg.

EXAMPLE 11

Three-day phases of daily unit dosages of EE 0.035 mg. and norgestimate 0.05 mg. alternating with daily unit dosages of EE 0.035 mg. and norgestimate 0.075 mg.

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EXAMPLE 12

Three-day phases of daily unit dosages of EE 0.035 mg. and norgestimate 0.05 mg. alternating with three-day phases of daily unit dosages of EE 0.035 and norgestimate 0.035 mg.

EXAMPLES 13 & 14

One formulation was administered to 2 women for a total of 3 cycles to establish that cycle control, in terms of breakthrough bleeding, is acceptable. The test formulation consisted of three daily unit dosages of 0.035 mg. of 17alpha-ethinylestradiol and 0.5 mg. of norethindrone alternating with three daily unit dosages of 0.035 mg. of 17alpha-ethinylestradiol and 0.75 mg. of norethindrone for a total of 7 groups of three, beginning and ending with the 0.5 mg. of norethindrone combination.

EXAMPLE 15

A 23 year old nulliparous woman who had not taken any hormonal formulation including oral contraceptives for three months agreed to take the test formulation of the invention for two cycles. The subject was in good health and did not smoke. The subject had no contraindications to the use of oral contraceptives and her menstrual cycles were regular. The subject started the test formulation on the fifth day of her cycle (onset of menstruation is considered day 1) for 21 consecutive days (first cycle), followed by a 7 day interval which was free of any hormone and then restarted the test formulation for another 21 days (second cycle). In the first cycle the subject had no bleeding or spotting while taking the test formulation and had a withdrawal bleed starting on the second day of the hormone free interval. The withdrawal bleed lasted for 5 days and was lighter than a normal menstrual

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period consisting of reddish-brown spotting. There was no discomfort associated with the withdrawal bleeding. In the second cycle, the subject was also free of bleeding or spotting while taking the test formulation and again had a brownish, very light withdrawal bleed which began two days after stopping the test formulation and lasted for 6 days. The subject experienced no side effects during the two test cycles.

EXAMPLE 16

The subject was a healthy, 27 year old nulliparous woman who was currently taking a commercially available oral contraceptive formulation containing 17alpha-ethiny- lestradiol and dl-norgestrel (Triphasil (Trade mark of Wyeth Pharmaceuticals)). The subject agreed to take the test formulation of the invention for one cycle. The subject started the test formulation after a 7 day hormone free interval following the last Triphasil tablet. The test formulation was taken for 21 days followed by a 7 day drug free interval. The subject had no spotting or bleeding during the time she took the test formulation and experienced a withdrawal bleed which began two days after stopping the test formulation. The withdrawal bleeding lasted four days, was painless and was the same amount and colour as a normal menstrual period for the subject. The subject had no side effects during the test formulation.

Both subjects found the test formulation to be acceptable in terms of cycle control, side effects and menstrual bleeding.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical preparation for contraceptive purposes comprising a series of from twenty to thirty-five consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of from two to four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity or an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, and the daily unit doses of said progestin dominant phases contain an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, the amount of said substance exhibiting progestin activity being alternately increased in the progestin dominant phases to provide daily unit doses exhibiting progestin dominant activity and decreased in the estrogen dominant phases to provide daily unit doses exhibiting estrogen dominant activity and wherein the amount of substance exhibiting estrogen activity per unit dose exhibits an estrogen activity equivalent to from about 0.02 to about 0.050 mg of 17α-ethinyl estradiol and the amount of substance exhibiting progestin activity per unit dose ranges from 0 to an amount which exhibits a progestin activity equivalent to about 1 mg of norethindrone and wherein each unit dose contains a pharmaceutically acceptable inert carrier when required.

2. A pharmaceutical preparation according to Claim 1, wherein all of said daily unit doses contain a uniform amount of said substance exhibiting estrogen activity.

3. A pharmaceutical preparation according to Claim 1, wherein the daily unit doses of said estrogen dominant phases are free of substance exhibiting progestin activity.

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4. A pharmaceutical preparation according to Claim 1, wherein said substance exhibiting estrogen activity is selected from the group consisting of 17α-ethinyl estradiol and said substance exhibiting progestin activity is selected from the group consisting of norethindrone, desogestrel, levo-norgestrel, norgestimate, progesterone, medroxy-progesterone acetate and gestodene.

5. A pharmaceutical preparation according to Claim 1, wherein said daily unit doses are in orally administrable form.

6. A pharmaceutical preparation according to Claim 1, wherein said daily unit doses are in transdermally administrable form.

7. A pharmaceutical preparation according to Claim 1, wherein said daily unit doses are in buccally administrable form.

8. A pharmaceutical preparation according to Claim 1, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of two daily unit doses each alternating with progestin dominant phases of two daily unit doses each.

9. A pharmaceutical preparation according to Claim 1, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of three daily unit doses each alternating with progestin dominant phases of three daily unit doses each.

10. A pharmaceutical preparation according to Claim 1, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of four daily unit doses each alternating with progestin dominant phases of three daily unit doses each.

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11. A pharmaceutical preparation according to Claim 1, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of three daily unit doses each alternating with progestin dominant phases of four daily unit doses each.

12. A pharmaceutical preparation according to Claim 1, wherein each of said daily unit doses contains an amount of substance exhibiting estrogen activity which exhibits an estrogen activity equivalent to from 0.02 to 0.05 mg of 17α-ethinyl estradiol, and an amount of substance exhibiting progestin activity ranging from 0 to an amount which exhibits a progestin activity equivalent to 1 mg norethindrone.

13. A pharmaceutical preparation according to Claim 12, wherein each of said daily unit doses contains an amount of substance exhibiting progestin activity which exhibits a progestin activity equivalent to from 0.2 to 1 mg norethindrone.

14. A pharmaceutical preparation according to Claim 12, wherein three unit dosages of 0.035 mg of 17α-ethinyl estradiol with 0.5 mg of norethindrone are alternated with three unit dosages of 0.035 mg of 17α-ethinyl estradiol with 0.75 mg of norethindrone.

15. A pharmaceutical preparation according to claim 12, wherein three unit dosages of 0.035 mg of 17α-ethinyl estradiol and 0.5 mg of norethindrone are alternated with three unit dosages of 0.035 mg of 17α-ethinyl estradiol and 0.35 mg of norethindrone.

16. A pharmaceutical preparation according to claim 12, wherein each estrogen dominant phase consists of two daily unit doses each containing 0.035 of 17α-ethinyl estradiol and 0.15 mg norethindrone, and each progestin dominant phase consists of

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two daily unit doses each containing 0.035 mg 17α-ethinyl estradiol and 0.5 mg norethindrone.

17. A pharmaceutical preparation according to Claim 12, wherein each estrogen dominant phase consists of three daily unit doses each containing 0.035 17α-ethinyl estradiol and 0.05 mg of norgestimate and the progestin dominant phase consists of three daily unit doses each containing 0.035 mg of 17α-ethinyl estradiol and 0.035 mg of norgestimate.

18. A pharmaceutical preparation according to claim 12, wherein each estrogen dominant phase consists of three daily unit doses each containing 0.035 mg 17α-ethinyl estradiol and 0.05 mg of norgestimate and the progestin dominant phase consists of three daily unit doses each containing 0.035 17α-ethinyl estradiol and 0.075 mg of norgestimate.

19. A contraceptive preparation for administration to a female of childbearing potential comprising repeating cycles of a contraceptive regimen, wherein each cycle comprises a total of twenty-eight consecutive daily unit doses, from twenty-one to twenty-four of which exhibit hormone activity and are arranged in alternating estrogen dominant phases and progestin dominant phases, each cycle ending with from four to seven hormone activity-free daily unit doses, each phase consisting of from two to four consecutive daily unit doses, wherein the daily unit doses contain an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, wherein the amount of said substance exhibiting progestin activity is alternately increased in the progestin dominant phases to provide daily unit doses exhibiting progestin dominant activity and decreased in the estrogen dominant phases to provide daily unit doses exhibiting estrogen dominant activity, and wherein the amount of substance exhibiting estrogen activity per unit dose exhibits an estrogen activity equivalent to from about 0.02 to about 0.050 mg of

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17α-ethinyl estradiol and the amount of substance exhibiting progestin activity per unit dose exhibits a progestin activity equivalent to from about 0.1 to about 1 mg of norethindrone, and wherein each unit dose contains a pharmaceutically acceptable inert carrier when required.

20. A pharmaceutical package for contraceptive purposes containing a total dosage regimen of from twenty to thirty-five consecutive daily unit doses arranged in said package in a fixed sequence corresponding to an intended order of administration in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of from two to four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity or an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, and the daily unit doses of said progestin dominant phases contain an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, the amount of said substance exhibiting progestin activity being alternately increased in the progestin dominant phases to provide daily unit doses exhibiting progestin dominant activity and decreased in the estrogen dominant phases to provide daily unit doses exhibiting estrogen dominant activity and wherein the amount of substance exhibiting estrogen activity per unit dose exhibits an estrogen activity equivalent to from about 0.02 to about 0.050 mg of 17α-ethinyl estradiol and the amount of substance exhibiting progestin activity per unit dose ranges from 0 to an amount which exhibits a progestin activity equivalent to about 1 mg of norethindrone, and wherein each unit dose contains a pharmaceutically acceptable inert carrier when required.

21. A pharmaceutical package according to Claim 20, wherein all of said daily unit doses contain a uniform amount of said substance exhibiting estrogen activity.

22. A pharmaceutical package according to Claim 20, wherein the daily unit doses of said estrogen dominant phases are free of substance exhibiting progestin activity.

23. A pharmaceutical package according to Claim 20, wherein said substance exhibiting estrogen activity is selected from the group consisting of 17α-ethinyl estradiol and said substance exhibiting progestin activity is selected from the group consisting of norethindrone, desogestrel, levo-norgestrel, norgestimate, progesterone and medroxy-progesterone acetate.

24. A pharmaceutical package according to Claim 20, wherein said daily unit doses are in orally administrable form.

25. A pharmaceutical package according to Claim 20, wherein said daily unit doses are in transdermally administrable form.

26. A pharmaceutical package according to Claim 20, wherein said daily unit doses are in buccally administrable form.

27. A pharmaceutical package according to Claim 20, containing a series of consecutive daily unit doses arranged in estrogen dominant phases of two daily unit doses each alternating with progestin dominant phases of two daily unit doses each.

28. A pharmaceutical package according to Claim 20, containing a series of consecutive daily unit doses arranged in estrogen dominant phases of three daily unit doses each alternating with progestin dominant phases of three daily unit doses each.

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29. A pharmaceutical package according to Claim 20, containing a series of consecutive daily unit doses arranged in estrogen dominant phases of four daily unit doses each alternating with progestin dominant phases of three daily unit doses each.

30. A pharmaceutical package according to Claim 20, containing a series of consecutive daily unit doses arranged in estrogen dominant phases of three daily unit doses each alternating with progestin dominant phases of four daily unit doses each.

31. The use of a pharmaceutical preparation for contraceptive purposes comprising a series of from twenty to thirty-five consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of from two to four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity or an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, and the daily unit doses of said progestin dominant phases contain an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, the amount of said substance exhibiting progestin activity being alternately increased in the progestin dominant phases to provide daily unit doses exhibiting progestin dominant activity and decreased in the estrogen dominant phases to provide daily unit doses exhibiting estrogen dominant activity and wherein the amount of substance exhibiting estrogen activity per unit dose exhibits an estrogen activity equivalent to from about 0.02 to about 0.050 mg of 17α-ethinyl estradiol and the amount of substance exhibiting progestin activity per unit dose ranges from 0 to an amount which exhibits a progestin activity equivalent to about 1 mg of

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norethindrone and wherein each unit dose contains a pharmaceutically acceptable inert carrier when required.

32. The use according to Claim 31, wherein all of said daily unit doses contain a uniform amount of said substance exhibiting estrogen activity.

33. The use according to Claim 31, wherein the daily unit doses of said estrogen dominant phases are free of substance exhibiting progestin activity.

34. The use according to Claim 31, wherein said substance exhibiting estrogen activity is selected from the group consisting of 17α-ethinyl estradiol and said substance exhibiting progestin activity is selected from the group consisting of norethindrone, desogestrel, levo-norgestrel, norgestimate, progesterone, medroxy-progesterone acetate and gestodene.

35. The use according to Claim 31, wherein said daily unit doses are in orally administrable form.

36. The use according to Claim 31, wherein said daily unit doses are in transdermally administrable form.

37. The use according to Claim 31, wherein said daily unit doses are in buccally administrable form.

38. The use according to Claim 31, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of two daily unit doses each alternating with progestin dominant phases of two daily unit doses each.

39. The use according to Claim 31, comprising a series of consecutive daily unit doses arranged in estrogen dominant

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phases of three daily unit doses each alternating with progestin dominant phases of three daily unit doses each.

40. The use according to Claim 31, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of four daily unit doses each alternating with progestin dominant phases of three daily unit doses each.

41. The use according to Claim 31, comprising a series of consecutive daily unit doses arranged in estrogen dominant phases of three daily unit doses each alternating with progestin dominant phases of four daily unit doses each.

42. The use according to Claim 31, wherein each of said daily unit doses contains an amount of substance exhibiting estrogen activity which exhibits an estrogen activity equivalent to from 0.02 to 0.05 mg of 17α-ethinyl estradiol, and an amount of substance exhibiting progestin activity ranging from 0 to an amount which exhibits a progestin activity equivalent to 1 mg norethindrone.

43. The use according to Claim 42, wherein each of said daily unit doses contains an amount of substance exhibiting progestin activity which exhibits a progestin activity equivalent to from 0.2 to 1 mg norethindrone.

44. The use according to Claim 42, wherein three unit dosages of 0.035 mg of 17α-ethinyl estradiol with 0.5 mg of norethindrone are alternated with three unit dosages of 0.035 mg of 17α-ethinyl estradiol with 0.75 mg of norethindrone.

45. The use according to Claim 42, wherein three unit dosages of 0.035 mg of 17α-ethinyl estradiol and 0.5 mg of norethindrone are alternated with three unit dosages of 0.035 mg of 17α-ethinyl estradiol and 0.35 mg of norethindrone.

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46. The use according to claim 42, wherein each estrogen dominant phase consists of two daily unit doses each containing 0.035 of 17α-ethinyl estradiol and 0.15 mg norethindrone, and each progestin dominant phase consists of two daily unit doses each containing 0.035 mg 17α-ethinyl estradiol and 0.5 mg norethindrone.

47. The use according to Claim 42, wherein each estrogen dominant phase consists of three daily unit doses each containing 0.035 17α-ethinyl estradiol and 0.05 mg of norgestimate and the progestin dominant phase consists of three daily unit doses each containing 0.035 mg of 17α-ethinyl estradiol and 0.035 mg of norgestimate.

48. The use according to claim 42, wherein each estrogen dominant phase consists of three daily unit doses each containing 0.035 mg 17α-ethinyl estradiol and 0.05 mg of norgestimate and the progestin dominant phase consists of three daily unit doses each containing 0.035 17α-ethinyl estradiol and 0.075 mg of norgestimate.

49. The use of a contraceptive preparation for administration to a female of childbearing potential comprising repeating cycles of a contraceptive regimen, wherein each cycle comprises a total of twenty-eight consecutive daily unit doses, from twenty-one to twenty-four of which exhibit hormone activity and are arranged in alternating estrogen dominant phases and progestin dominant phases, each cycle ending with from four to seven hormone activity-free daily unit doses, each phase consisting of from two to four consecutive daily unit doses, wherein the daily unit doses contain an amount of a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity, wherein the amount of said substance exhibiting progestin activity is alternately increased in the progestin dominant phases to provide daily unit doses exhibiting progestin dominant activity and decreased

in the estrogen dominant phases to provide daily unit doses exhibiting estrogen dominant activity, and wherein the amount of substance exhibiting estrogen activity per unit dose exhibits an estrogen activity equivalent to from about 0.02 to about 0.050 mg of 17α-ethinyl estradiol and the amount of substance exhibiting progestin activity per unit dose exhibits a progestin activity equivalent to from about 0.1 to about 1 mg of norethindrone, and wherein each unit dose contains a pharmaceutically acceptable inert carrier when required.

50. A contraceptive preparation for administration to a woman comprising a series of from 20 to 35 consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of at most four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity sufficient to promote the development of progestin receptors in the endometrium of a woman to whom said preparation is administered, and the daily unit doses of said progestin dominant phases contain said substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity sufficient to antagonize the effect of estrogen on the endometrium of a woman to whom said preparation is administered and wherein each daily unit dosage includes a pharmaceutically acceptable inert carrier when required.

51. A preparation as claimed in claim 50 wherein each phase comprises from two to four unit dosages.

52. A contraceptive package containing a total dosage regimen of 20 to 35 consecutive daily unit doses in orally administrable tablet form arranged in said package in a fixed sequence corresponding to an intended order of administration in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of at most four consecutive daily

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unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity sufficient to promote the development of progestin receptors in the endometrium of a woman to whom said doses are administered, and the daily unit doses of said progestin dominant phases contain substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity sufficient to antagonize the effect of estrogen on the endometrium of a woman to whom said doses are administered and wherein each daily unit dosage includes a pharmaceutically acceptable inert carrier when required.

53. A package as claimed in claim 52 wherein each phase comprises from two to four unit dosages.

54. The use of a contraceptive formulation for administration to a woman of childbearing age comprising a series of from 20 to 35 consecutive daily unit doses arranged in alternating estrogen dominant phases and progestin dominant phases, each phase consisting of at most four consecutive daily unit doses, wherein the daily unit doses of said estrogen dominant phases contain an amount of a substance exhibiting estrogen activity sufficient to promote the development of progestin receptors in the endometrium of said woman, and the daily unit doses of said progestin dominant phases contain a substance exhibiting estrogen activity and an amount of a substance exhibiting progestin activity sufficient to antagonize the effect of estrogen on the endometrium of said woman and wherein each daily unit dosage includes a pharmaceutically acceptable inert carrier when required.

55. The use of a contraceptive formulation as claimed in claim 54 wherein each phase comprises from two to four unit dosages.

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SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente